REMARKS

Information Disclosure Statements

Applicants thank the Examiner for acknowledgment of the Supplemental Information Disclosure Statement (SIDS) filed on May 22, 2001. However, an IDS was also mailed on March 29, 2001. Enclosed is a copy of the relevant postcard receipt, dated April 2, 2001 by the U.S. Patent and Trademark Office. Acknowledgment of the information contained in the IDS mailed March 29, 2001 is respectfully requested. Applicants will forward a copy of the IDS to assist the Examiner if necessary.

Claim Amendments

Claims 22, 32 and 42 have been amended to recite "identity of at least one nucleotide position of a polynucleotide of interest" is determined. Support for this amendment is found in the claims as originally filed and in the specification, for example, at page 7, line 26 through page 8, line 12 and page 10, lines 6-16. Claims 22 and 42 have also been amended to clarify that nucleotide sequence is determined.

Claim 32 has been amended to clarify that the oligonucleotides hybridize immediately adjacent to the potential alterations and to delete "and" at the end of step c).

Claim 42 has been amended to clarify that the sets of oligonucleotides comprise one or more oligonucleotides and that at least one set comprises at least two oligonucleotides that are substantially homologous but differ from each other by one base at their 3′ termini. Support for this amendment is found in Figure 1 and, for example, in the specification at page 6, lines 20-23.

Double Patenting

The Examiner has rejected Claims 22-53 under the judicially created doctrine of obviousness-type double patenting. The conflicting patent is co-owned with the instant application. A Terminal Disclaimer and Statement Under 37 C.F.R. § 3.73(b) executed by co-owner Pharmacia Biotech AB is being concurrently filed herewith with the appropriate fee. A Terminal Disclaimer and Statement Under 37 C.F.R. § 3.73(b) executed by co-owner Baylor College of Medicine will be filed as a Supplemental Response as soon as an executed copy is received by Applicants' Agent.

Withdrawal of the rejection is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 42-50 under 35 U.S.C. § 102(e) as being anticipated by Goelet *et al.* (U.S. Patent 6,004,744). The Examiner stated that Goelet *et al.* teach a method that comprises "contacting a polynucleotide of interest with an array of a set of primers wherein the oligonucleotides differ by at least one base at the 3′ end (. . .)".

Applicants respectfully traverse this rejection.

Goelet *et al.* do not anticipate Claims 42-50 because Goelet *et al.* do not teach each and every element of Claim 42. Goelet *et al.* predominantly show single primers. When multiple primers are shown, Goelet *et al.* teach primers that differ completely from each other because they are intended for hybridization with different template molecules (see Figures 9-11 and Col. 23).

In contrast, the claimed invention is drawn to arrays of oligonucleotides that comprise sets of primers wherein the oligonucleotides of a set differ from each other by one base at their 3′ termini. Claim 42 has been amended to clarify that at least one set of the array comprises at least two oligonucleotides that are substantially homologous but differ from each other by one base at their 3′ termini. Support for this amendment is described above.

Goelet *et al.* do not teach or suggest the use of a set of primers that comprises at least two oligonucleotides that are substantially homologous, but differ from each other by one base at their 3′ termini. Claims 43-50 are dependent upon Claim 42 and have all of the elements of Claim 42. Therefore, Goelet *et al.* do not anticipate any one of Claims 42-50.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 22-52 under 35 U.S.C. § 103(a) as being unpatentable over Goelet *et al.* in view of Rust *et al.* (U.S. Patent 5,605,794). The Examiner stated that Goelet *et al.* do not expressly teach the use of primers with different lengths. However, the Examiner stated that "it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Goelet *et al.* with the use of primers of

different lengths as taught by Rust *et al.*, since Rust *et al.* expressly motivates the use of different length primer in order to achieve specific detection of extension products."

Applicants respectfully traverse the rejection.

Claims 22, 32 and 42 are drawn to methods wherein the nucleotide sequence or identity of at least one nucleotide of a polynucleotide of interest is determined. Each of Claims 22, 32 and 42 as originally filed included a step of identifying each terminating nucleotide that had been added to each primer. Claims 22 and 42 have been amended to clarify that the claimed invention is a method for determining nucleotide identity of at least one nucleotide position of a polynucleotide of interest. Claim 32 has been amended to clarify that nucleotide identity of at least one nucleotide position of the polynucleotide of interest is determined.

The combination of Goelet *et al.* and Rust *et al.* do not render the claimed invention obvious, because neither of these references teach or suggest the claimed invention and the asserted combination of Goelet *et al.* and Rust *et al.* fails to consider the teachings of those references as a whole. When considered as a whole, no motivation for the combination of teachings of Goelet *et al.* and Rust *et al.* exists.

As noted by the Examiner, Goelet *et al.* do not disclose or suggest use of primers of different lengths. However, Goelet *et al.* not only fail to disclose or suggest the use of primers of different lengths, Goelet *et al.* teach away from primers of different lengths. Goelet *et al.* expressly teach that their method avoids the need for gel electrophoretic size separation of the nucleic acid species (Col. 4, lines 51-54). Goelet *et al.* teach that specific benefits are afforded by their method with the particular feature of avoiding gel electrophoretic size separation (Col. 4, lines 54-57). In particular, Goelet *et al.* teach that avoiding gel electrophoretic size separation renders the process easily adaptable to automation and permits the analysis of large numbers of samples at relatively low cost (*Id.*). Furthermore, the specific method taught and exemplified by Goelet *et al.* as having these advantages involves affinity separation of primers (Col. 15, lines 9-10 and Col. 23, lines 1-42). According to Goelet *et al.*, more than one oligonucleotide can be separated and analyzed simultaneously if more than one affinity group is used (Col. 15, lines 12-14). Goelet *et al.* teach that the use of affinity group-labeled oligonucleotides "eliminates the need of physical or size separation" (Col. 15, lines 10-11). Therefore, when read as a whole, Goelet *et al.* teach away from the use of primers of different lengths.

Furthermore, extraction of the teaching of length alone from the carefully designed competitive primers of Rust *et al.* fails to consider the teachings of Rust *et al.* as a whole or even the passage cited by the Examiner when taken in context with the surrounding descriptive portion of the specification. A complete reading of Rust *et al.* as a whole reveals that the primers of Rust *et al.* are for a completely different purpose than the primers as disclosed in the presently claimed invention. Rust *et al.* teach a type of competitive priming assay that uses PCR amplification in conjunction with specially designed primers. The result is amplification of specific segments of nucleic acid, where the detection of the product indicates the presence or quantity of the target sequence of interest (Col. 11, lines 4-11; Col. 3, lines 15-36).

As stated in the Rust *et al.* passage at Col. 11, lines 4-11, the oligonucleotides are distinguished by a feature other than different length. The specially designed primers of Rust *et al.* span the nucleotide position of interest and require at least two site specific primers for each site of interest. The primers are distinguished because one primer has a match at the site of interest, and the other has a mismatch at the site of interest. In addition, each site specific primer of the set has a mismatch with the target sequence at a site distinct from the nucleotide position of interest. Depending on the number of mismatches, a product will or will not be amplified. Depending on the presence or absence of product, the presence or quantity of target sequence is revealed. The method of Rust *et al.* does not result in any nucleotide sequence identification, and certainly no sequence identification of the site of interest. The Examiner has provided no motivation to extract the teaching of length from Rust *et al.* which is taught as useful for detection or quantification of target sequence, and to combine it with the teaching of Goelet *et al.* to produce Applicants' claimed invention.

Teachings taken out of context indicate that the Applicants' own invention has improperly been used as a blueprint to assemble elements in the prior art in an attempt to establish *prima facie* obviousness. It is well settled that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,* 230 USPQ 416, 419 (CAFC 1986). In *Bausch & Lomb,* the court overturned a finding of obviousness that was based on the use of a single line out of the prior art.

In that case, the court did not deny that the cited line stated the elements asserted to be obvious; however, the court found that the line was taken out of context. The *Bausch & Lomb* court reasoned that because the teaching of the secondary reference was taken out of context, improper hindsight had been used to find obviousness. *Bausch & Lomb, Inc.* 230 USPQ at 419, 420.

Like *Bausch & Lomb, Inc.*, the teaching of the different lengths of oligonucleotides described by Rust *et al.* is taken completely out of context with the teachings of Rust *et al.* as a whole as well as with the portion of the specification with the passage containing the alleged teaching. Rust *et al.* teach

> the specific detection of extension products, which is a measure for the presence or the quantity of the nucleic acid to be detected in the sample is, for example, also possible by making use of the fact that the oligonucleotides used could be discriminated by one more feature . . . for example, the varying lengths of oligonucleotides of one set. The extension of different oligonucleotides then produced products of different length (Col. 11, lines 4-11, emphasis added).

Rust *et al.* do not disclose or suggest the use of primers for sequencing. Rust *et al.* do not disclose or suggest a method of sequencing. Furthermore, the primary reference (Goelet *et al.*) teach away from the use of primers of different lengths in sequencing reactions as presently claimed. There is no motivation in Rust *et al.* to modify the teaching away of Goelet *et al.* because Rust *et al.* addresses a completely different problem compared to Goelet *et al.* and when compared to the claimed invention.

There is simply no disclosure or suggestion in the prior art of using primers of different lengths for determining nucleotide sequence as presently claimed. The suggestion, either explicit or implicit, of substituting one element for another in the prior art must be founded on the prior art and not obtained from the Applicants' disclosure. *In re Vaeck,* 20 USPQ2d 1439, 1442, 1444 (CAFC 1991). The primary reference of *In re Vaeck* taught all but one element of the claimed invention. The primary reference taught the expression of a CAT marker gene in cyanobacteria, while the secondary reference taught the expression of insecticidal *Bacillus* genes in two different *Bacillus* species. The *Vaeck* court reversed an obviousness rejection of claims drawn to the expression of insecticidal *Bacillus* genes in cyanobacteria because the court found no suggestion in the prior art for the substitution of the gene in the primary reference for the gene in the secondary reference. Similarly, there is no suggestion in either Goelet *et al.* or Rust *et al.*,

taken separately or in combination, for substituting the primers of Goelet *et al.* having the same length with the oligonucleotides of Rust *et al.* or in making the primers of Goelet *et al.* with variable length taken from Rust *et al.*

Even when the change is a simple one, such as inverting a prior art container base, the Examiner must provide evidence that the prior art fairly suggested the desirability of making the simple change. *Continental Can Co. USA Inc. v. Monsanto Co.* 20 USPQ2d 1746, 1751 (CAFC 1991). The is no evidence of the desirability of using primers of different lengths in the method of Goelet *et al.* because Goelet *et al.* teach away from such a modification and because the Rust *et al.* method does not even involve sequencing or identifying nucleotide sequence as presently claimed.

The combination of Goelet *et al.* and Rust *et al.* fails to render the claimed invention obvious. Goelet *et al.* teach away from use of primers of different lengths and the teaching of Rust *et al.* is taken completely out of context, a clear indication of hindsight analysis. Therefore, no motivation is shown for combining the teachings of Goelet *et al.* and Rust *et al.* to render Applicants' claimed invention obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By _____

Sandra A. Brockman
Registration No. 44,045
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: April 10, 2002

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R § 1.121(c)(1)(ii)

22. (Amended) A method of [analyzing a nucleotide sequence] determining nucleotide identity of at least one nucleotide position of a polynucleotide of interest, comprising the steps of[:];

a) contacting the polynucleotide of interest with a population of single-stranded primers, wherein said population of single-stranded primers comprises at least two oligonucleotides of different lengths, wherein said oligonucleotides have known sequences, such that at least [two] one oligonucleotide[s] hybridizes to the polynucleotide of interest immediately adjacent to [one or more nucleotides] each nucleotide position of interest to be identified, generating template-single-stranded primer complexes;

b) subjecting said complexes to a single base extension reaction to extend each hybridized primer by a terminating nucleotide, generating extended primers;

c) separating said extended primers from each other; and

d) identifying each terminating nucleotide that has been added to each extended primer, thereby determining the identity of at least one nucleotide position of a polynucleotide of interest.

32. (Amended) A method of analyzing a nucleotide sequence of a polynucleotide of interest for the presence or absence of one or more alterations, wherein the sequence of the polynucleotide of interest is generally known, and wherein nucleotide identity of at least one nucleotide position of a polynucleotide of interest is determined, comprising the steps of;

a) contacting said polynucleotide of interest with a population of single-stranded primers, wherein said population of single-stranded primers comprises at least two oligonucleotides of different lengths and wherein said oligonucleotides have known sequences, such that at least one [two] oligonucleotide[s] hybridizes immediately adjacent to [said one or more] each potential alteration[s, if present,] in the polynucleotide of interest, generating template-single-stranded primer complexes;

b) subjecting said complexes to a single base extension reaction to extend each hybridized primer by the addition of a terminating nucleotide, generating extended primers;

c) separating said extended primers from each other; [and]

d) identifying each terminating nucleotide that has been added to each extended primer[,]; and

e) comparing said identified nucleotide with the sequence of the polynucleotide of interest, [thereby determining]whereby the presence or absence of one or more alterations is determined.

42. (Amended) A method [of analyzing a] for determining nucleotide identity of at least one nucleotide position [sequence] of a polynucleotide of interest, comprising the steps of:

a) contacting said polynucleotide of interest [to] with a population of single-stranded primers, wherein said single-stranded primers comprise an array of one or more sets of one or more oligonucleotides, wherein [the] at least one set comprises at least two oligonucleotides [of a set] that are substantially homologous but differ from each other by one base at [the] their 3' termini, [end and] wherein [said] the oligonucleotides of the array have known sequence and wherein each [said] oligonucleotide [having known sequence] is attached to a solid support at a known location, to form the array, wherein at least one oligonucleotide of the array hybridizes to said polynucleotide of interest immediately adjacent to [one or more nucleotides] each nucleotide position to be identified, generating template-single-stranded primer complexes;

b) subjecting said complexes to a single base extension reaction to extend each annealed primer by a terminating nucleotide, generating extended primers; and

c) identifying each terminating nucleotide that has been added to each primer; thereby determining the identity of at least one nucleotide position of a polynucleotide of interest.